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Appendix

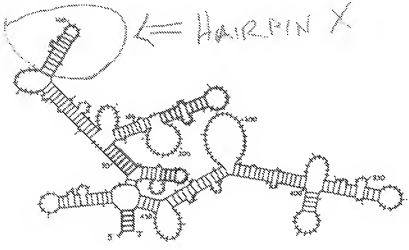

Figure 3 : Folding of an immunoglobulin γ1 heavy chain mRNA fragment. The heavy lines indicate base pairings which coincide with those found by Rogers *et al.* (11). Our folding of this 459 nucleotide fragment found a structure with a 15 % energy improvement (-181.6 kcal/mole, vs. -158.5 kcal/mole for Rogers *et al.*) in 1½ seconds.

not occur in our simpler yet more powerful algorithm. No compromises are made to save time ; they are not needed. The 15 % improvement in minimum free energy is therefore not surprising, since we solved the problem precisely as stated. More noteworthy is the almost complete lack of similarity between our computed structure and the best folding proposed by Rogers *et al.* (11). In figure 3, the base pairing regions which occur in both proposed foldings are shown by heavier lines. Only 29 % of the base pairings in our structure can be found in the corresponding one by Rogers *et al.* We do not claim that the structure we have produced is better than theirs. This example was given mainly to illustrate the power of our method. The deeper question raised by it is how to choose one proposed folding over an other.

5. Suboptimality and additional information.

The words 'optimal structure' refer to a folding of minimum free energy. Such a structure is not necessarily unique. With molecules the size of 5S ribosomal RNA's or greater, and with the rather intricate energy function used, computing energies to the tenth of a kcal/mole, it is unlikely to have two or more optimal structures of exactly the same energy, but it can happen.